

The Action of Sulphur and Selenium on 6-Benzal-
amino, 2-Phenyl Benzoselenazole. Synthesis
of an Analog of Cinchophen



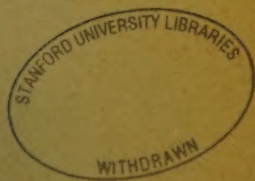
DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
THE FACULTY OF PURE SCIENCE OF
COLUMBIA UNIVERSITY

BY

HORACE H. HOPKINS, B.S.

NEW YORK CITY
1924



3781
72H

UNCLASSIFIED

Dissertation

The Action of Sulphur and Selenium on 6-Benzal-
amino, 2-Phenyl Benzoselenazole. Synthesis
of an Analog of Cinchophen

DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
THE FACULTY OF PURE SCIENCE OF
COLUMBIA UNIVERSITY

BY

HORACE H. HOPKINS, B.S.

NEW YORK CITY

1924

TO LAURA LEE HOPKINS, MY WIFE, THIS RESEARCH
IS AFFECTIONATELY DEDICATED

ACKNOWLEDGEMENT

The author desires to express his appreciation and gratitude for the valuable suggestions and criticisms of Professor Marston Taylor Bogert in the prosecution of this research.

The Action of Sulphur and Selenium on 6-Benzalamino, 2-Phenyl Benzoselenazole. Synthesis of an Analog of Cinchophen

ABSTRACT OF DISSERTATION

Purpose of the Research

To study the chemistry of sulphur and selenium in heterocyclic union with a view to exploration of the pharmacological properties of selenium in organic compounds.

Method of Attack

Starting with 6-amino and 6-benzalamino, 2-phenyl benzoselenazole, a carboxyl derivative analogous to atophan, and thiazole and selenazole derivatives of 2-phenyl benzoselenazole were prepared and their chemical properties studies.

Results Obtained

- a*—A soluble salt of the 6-carboxyl derivative of 2-phenyl benzoselenazole has been prepared which is an analog of the valuable cinchoninic acid used in the treatment of gout.
- b*—With the synthesis of 2, 2'-diphenyl benzo bis selenazole a new type of heterocyclic selenium compounds with two atoms of selenium in the nucleus has been prepared. The bis selenazole was synthesised in two ways. Several derivatives have been prepared and are listed below.
- c*—The synthesis of 2, 2'-diphenyl thiazolylbenzo selenazole presents another new heterocyclic type, combining in a single compound both thiazole and selenazole structures. The thiazolyl selenazole can be acetylated, and nitrated, and readily adds bromine to form an unstable addition compound.
- d*—The following new compounds have been prepared:
 - 6-cyano 2-phenyl benzo selenazole.
 - 6-carboxy 2-phenyl benzo selenazole.
 - Methyl ester of 6-carboxy 2-phenyl benzo selenazole.
 - Potassium salt of 6-carboxy 2-phenyl benzo selenazole.
 - 6-furfurylidene-amino 2-phenyl benzo selenazole.
 - 2, 2'-diphenyl benzo bis selenazole.
 - Dinitro 2, 2'-diphenyl benzo bis selenazole.
 - Mononitro 2, 2'-diphenyl benzo bis selenazole.

Tetrabrom addition product of 2, 2'-diphenyl thiazolyl benzo selenazole.

INTRODUCTORY AND HISTORICAL

In 1913, B. G. Duhamel (20, 21) called attention to the physiological effects produced by the introduction of colloidal selenium into the bloodstream of rabbits. No active poisoning resulted when moderate doses of the colloid were administered. Walker (24) later corroborated the non-poisonous character of selenium itself. He also found that injections of colloidal selenium produced no effects upon tumors.

Hydrogen selenide is much more toxic than hydrogen sulphide. Clark and Hurtley (11) found that the action of hydrogen selenide upon blood is analogous to that of hydrogen sulphide (8). The selenium replaced the oxygen of the hemoglobin to form a seleno-hemoglobin. Wassermann and Hausmann (15) claimed that injections of sodium selenide into mouse tumors caused these to disappear. Hantzlik and Tarr (45) investigated the physiological properties of various organic selenides, such as dichlor ethyl selenide, and found that these selenides were excellent skin irritants. Swelling, hyperemia, necrosis, and vesication resulted from external application.

Of the diselenides, diantipryl diselenide and diselenides of the anthraquinone series (42, 31) have been suggested as having therapeutic value.

As early as 1890, C. Chabrie (7) noted the toxic effects of selenious acid and selenites. A dose of 3 milligrams of acid per kilo weight sufficed to kill dogs. Other investigators have corroborated this work (12, 24). Selenates are reduced in the animal organism to selenites. Jones (12, 17) found that the animal body endeavors to throw off selenite poison by reduction of the selenite to red amorphous selenium, which collects in reddish brown spots in the tissues. Glycogen, glucose, and fats are apparently the reducing agents, since the content of these substances in the body decreases rapidly in animals that have been poisoned with selenites. Proteins seem to take no part in the reaction.

Wassermann, Keyser, and Fasiani have studied the physiological action of selenites and selenates upon cancerous growths. The former (13) noted that sodium selenite destroyed tumor cells, when injected directly into the growth. Fasiani (23) stated that selenites and selenates increase the rate of autolysis of both sarcoma and carcinoma taken from man.

Selenoureas are too unstable to find usage as medicinals. However, several alkyl halide addition products of allyl seleno-carbamide have been patented (43, 44) on the basis of claims of therapeutic value.

Isoselenazoles of the anthraquinone series have shown promise of therapeutic value according to the Baeyer Company (30).

The physiological action of the other selenazoles has not been investigated.

Since amino substituted oxazine and thiazine dyestuffs, such as methylene blue, have well known medicinal value, several attempts have been made to synthesise and investigate selenium analogs. P. Karrer (39) described the synthesis of seleno methylene blue and ascribed marked bactericidal properties to it. Other selenium analogs of the thiazines are noted in the bibliography (28, 29, 33). All claim therapeutic value. Karrer has synthesised a p-phenyl arsinic acid derivative of selenazine that showed strong bactericidal action (39). Karrer observed that no toxic effects, characteristic of H_2Se or H_2SeO_3 , were observed when selenazines were administered. He concluded that the selenazine ring was too stable to be broken down by the animal organism.

Seleno-eosin preparations have been the subject of some dispute as to their therapeutic value. In 1911, A. and E. Wassermann (13) called attention to the physiological action of a seleno-eosin preparation upon mouse tumors. These dyestuffs were introduced in amounts up to one part in two hundred parts of water without fatal results to the mice (13, 38). Complete resorption of some tumors occurred, the sarcoma disappearing more rapidly than carcinoma. Walker, however, stated that the Wassermann eosin preparations have no selective action on tumor cells (24). Keyser, Coenen and Schuleman (34, 36) found a curative effect upon subcutaneous mouse tumors. The preparations were inert against tumor cells in test tube trials. Keysser then concluded that the marked effect upon the subcutaneous cancers, was due to the injury to these produced by too frequent handling and examination.

Ehrlich and Bauer (37) have synthesised 3, 6 diamino seleno pyronine which has a toxicity less pronounced than its sulphur analog. Pronounced edema resulted from the introduction of the dyestuff into the animal bodies.

Seleno saccharine and seleno saccharides have been prepared (16, 40, 47, 51). The seleno saccharine has not the characteristic sweet taste of its sulphur analog. The physiological effects of these compounds were not described.

DISCUSSION

With a view to preparing a selenium analog of the well known cinchophen or atophan, 6-amino 2-phenyl benzo selenazole was diazotised and converted into the corresponding acid which was esterified to obtain it in pure form. The methyl ester was saponified and yielded a potassium salt which was soluble to about one

per cent in aqueous solution. The aqueous solution of the salt yielded precipitates with the heavy metal ions, barium and ammonium ions.

Experimental evidence (32, 49) has shown that the physiological activity of atophan or 2-phenyl cinchoninic acid is apparently due to the presence of the 2-phenyl group on the quinoline nucleus. Hofman (3) and Jacobson (4) have called attention to the chemical similarities between the quinoline and benzo thiazole nuclei. An analogous chemical similarity exists with the selenazoles. Sulphur and selenium can displace an ethylene group in cyclic union without materially affecting the chemical character of the compound. By structural analogy, therefore, the 2-phenyl benzo selenazole nucleus may act physiologically like the 2-phenyl quinoline nucleus occurring in atophan.

Because of its water solubility the salt of the 6-carboxyl derivative of 2-phenyl benzo selenazole may be used to test the physiological action of this selenazole conformation.

Attempts to fuse selenium with para nitro benzylidene para toluidine (2) and para amino benzylidene para toluidine (9) to form the corresponding selenazoles, failed. The Schiff bases proved too unstable to stand the heat of fusion, and only decomposition occurred.

In the purification of 2-phenyl benzo selenazole, a marked improvement in the technique was introduced by the vacuum distillation of the crude acid extracts of the tar and subsequent crystallization of the distillate. This method eliminates the many crystallizations and bone blackings formerly required to give a pure product.

Seleno benzamide was prepared by the method described by Becker and Meyer (10). The product consisted of gleaming golden needles which decomposed on standing. No work was attempted with this compound.

Furfuraldehyde condensed with 6-amino 2-phenyl benzo selenazole to give a crystalline fural Schiff base which is too unstable to react by fusion with sulphur or selenium.

2, 2'-diphenyl benzo bis selenazole has been prepared in two ways. The preparation from para phenylene diamine proves that the amino group of the amino 2-phenyl benzo selenazole is in the 6 position. The bis selenazole is a monacid base, adding but one molecule of acetyl chloride. It can be nitrated so readily that a mono nitro derivative was not obtained free from the dinitro compound. The impure mononitro derivative upon reduction yielded an amine which was very hard to purify from the tarry reduction by-products. The amine yields a crystalline

benzal derivative when dissolved in a small amount of hot benzaldehyde and allowed to cool. A pure dinitro derivative of the benzo bis selenazole was obtained by use of a slight excess of acid in the nitrating mixture.

Analogous in structure and properties to the bis selenazole is the 2, 2'diphenyl thiazolyl benzo selenazole which was prepared by fusing sulphur with 6-benzalamino 2-phenyl benzo selenazole. Like the bis selenazole, it is a monacid base, adding but one molecule of acetyl chloride. It can be nitrated readily yielding a dinitro derivative. Treated with bromine, it adds four atoms of halogen to yield an unstable addition product which decomposes gradually on standing. Attempts to prepare a methyl iodide addition product failed.

One fusion of 6-benzalamino 2-phenyl benzo selenazole with sulphur yielded, instead of the thiazolyl selenazole, a base of the empirical formula $C_{27}H_{18}N_2S_2Se$. This product closely resembled the thiazolyl selenazole in appearance and solubility. It yielded a dinitro derivative of the empirical formula $C_{27}H_{16}N_4O_4S_2Se$, which upon reduction, lost an atom of sulphur to give a diamine of the formula $C_{27}H_{20}N_4SSe$. Insufficient material was available to establish the structure of these compounds.

EXPERIMENTAL PART

2-Phenyl benzo selenazole—This compound was prepared by the method of Bogert and Chen (55), by fusing benzalaniline with selenium on a sand bath for three days. The resultant tar was extracted with hot concentrated HCl , and the selenazole precipitated by dilution. The dry precipitate instead of being repeatedly recrystallized from ethyl alcohol to free it from impurities, was distilled in vacuo and the distillate crystallized once. The product melted at 117.5° corr. in agreement with that obtained by Bogert and Chen. The selenazole distilled readily at 220° - 230° under 28 mm. pressure.

6-Nitro 2-phenyl benzo selenazole—Fifty gram lots of the 2-phenyl benzo selenazole were nitrated in the usual way. It was found advantageous to recrystallize the nitro derivative from normal butyl alcohol in which the nitro selenazole is much more soluble than in ethyl alcohol, the solvent used by Bogert and Chen. The melting point of the product was 202° - 203° corr. Bogert and Chen give 202.4° corr.

6-Amino 2-phenyl benzo selenazole—The nitro derivative was reduced by tin and hydrochloric acid. The seventy per cent yields and melting point of 201.3° to 202.3° corr. of the product obtained were the same as given by Bogert and Chen for this compound. Ethyl alcohol was used as the crystallizing medium.

6-Cyano 2-phenyl benzo selenazole.—Ten grams of copper sulphate crystals were dissolved in 40 c.c. of water. To this solution a solution of 12 grams of potassium cyanide in 20 c.c. of water was added. Ten grams of the 6-amino selenazole were suspended in 25 c.c. of hydrochloric acid and 30 c.c. of water; this being diazotised by slowly adding a solution of 5 grams of sodium nitrite in 20 c.c. of water, the mixture being immersed in an ice salt bath. The suspension of diazotised amine was slowly added to the boiling potassium cuprocyanide solution, the nitrile precipitating at once. After heating for a half hour, the mixture was filtered, washed, and dried. A yield of 12 grams of a brown powder was obtained. Attempts to purify it by crystallization from ethyl and normal butyl alcohols, carbon tetrachloride, acetone and benzene failed. The product sintered and decomposed from 145° to 153°.

2-Phenyl benzo selenazole 6-carboxylic acid.—The crude nitrile from the Sandmeyer reaction was boiled under a reflux condenser with a mixture of 50 c.c. of concentrated H_2SO_4 and 25 c.c. of water. After twenty-two hours of refluxing, the solution was diluted with 100 c.c. of water. The precipitate was filtered, washed with water and suspended in warm dilute potassium hydroxide and again filtered. The clear filtrate was acidified with HCl to precipitate the free acid, which was filtered, washed and dried. Yield 4.9 grams or 36 per cent. of theory. The yellow powder could not be crystallized by solution in ethyl alcohol, ethyl acetate, acetone or benzene. By alternate solution in alkali and reprecipitation with HCl, it was purified to a lighter color but could not be obtained pure enough for an analysis.

Methyl ester of 2-phenyl benzo selenazole 6-carboxylic acid.—The crude yield of acid from the hydrolysis was suspended in 50 c.c. of absolute methyl alcohol which had been saturated with dry HCl gas. A current of gas was passed through the suspension for four hours, the mixture being heated in a bath maintained at 80°. The suspension was then filtered on an asbestos mat to remove undissolved material and then diluted with 150 c.c. of water. The precipitate obtained, was filtered, washed and suspended in dilute sodium carbonate solution. It was then filtered, washed and dried. Yield, 1.7 grams of crude product. This was repeatedly recrystallized with bone blacking from ethyl alcohol to give yellow plates melting at 164.5° to 165.5° corr. Yield pure product 0.5 gram or 10 per cent.

Analysis	Subs.	0.1816;	CO_2 ,	0.3765;	H_2O ,	0.0580
	Calc. for	$\text{C}_{15}\text{H}_{11}\text{NO}_2\text{Se}$:	C,	56.93;	H,	3.48
	Found		C,	56.55;	H,	3.55

An attempt was made to convert the nitrile directly to the ester by dissolving the crude nitrile yield in 50 c.c. of absolute methyl alcohol, 5 c.c. of water, and 55 gms. of concentrated H_2SO_4 (48). After refluxing for eight hours, the solution was diluted with 150 c.c. of water and filtered. The precipitate yielded five grams of Na_2CO_3 soluble solid and three grams of insoluble solid. By repeated crystallization from ethyl alcohol with bone blacking 0.3 gm. of pure ester was isolated. The ester is soluble in hot ethyl and butyl alcohol, acetone, acetic acid, and benzene.

Potassium salt of 2-phenyl benzo selenazole 6-carboxylic acid—One gram of the pure ester was dissolved in twenty c.c. of alcohol and 3 c.c. of a 20 per cent solution of KOH in alcohol added. The pink tinged salt separated out at once as a fine granular precipitate. It was filtered and washed with alcohol and dried. The salt is quite soluble in alcohol and alcohol-water mixtures. It is soluble in water to about one per cent. Yield 0.5 gm. or about 50 per cent. The aqueous solution of the salt yields precipitates with the following ions: Ba^{++} , NH_4^+ , Ni^{++} , Mg^{++} , Ca^{++} , Fe^{+++} , Al^{+++} , Pb^{++} , Cu^{++} .

Analysis: Subs. 0.1560; CO_2 , 0.2811; H_2O , 0.0363
Calc. $\text{C}_{14}\text{H}_8\text{NO}_2\text{KSe}$: C, 49.38; H, 2.37
Found C, 49.14; H, 2.60

Attempted fusion of paranitro benzylidene para toluidine—Paranitro benzaldehyde was prepared by the oxidation of paranitro toluene with chromyl chloride according to the method of V. von Richter (2). Sixty grams of the paranitro toluene yielded 50 grams of the aldehyde. The chromyl chloride was prepared by Moles and Gomez method (14) of heating a mixture of sodium chloride, potassium bichromate and fuming sulphuric acid. Forty per cent yields of redistilled chromyl chloride boiling at 116° corr. were obtained.

The para nitro benzylidene para toluidine was prepared by heating the aldehyde and toluidine together in molecular proportions at about 140° . To 50 grams of this Schiff base, 40 grams of selenium were added and a fusion attempted. In spite of very careful heating, charring and decomposition occurred before any reaction set in. The repeated attempts were failures.

Attempted fusion of para amino benzylidene para toluidine with selenium—In another attempt to prepare a 2-phenyl benzo selenazole with a substituent on the 2-phenyl nucleus, the amino derivative of the above Schiff base was fused with selenium. While para amino benzylidene para toluidine has been prepared from the nitro derivative and is described in a German patent (9),

no details of the reduction of the nitro Schiff base were available. It was prepared by a reduction with sodium sulphide. Fifty-seven grams of the nitro Schiff base were dissolved in a solution containing 16 grams of sulphur and 64 grams of sodium sulphide in 240 c.c. of alcohol and 52 c.c. of water. After three hours refluxing the alcohol was evaporated and 500 c.c. of water added. The resultant mixture was extracted with ether and the ether extracts evaporated on a steam bath. Fifty-two grams of a red non distillable oil remained which in appearance corresponded with the para amino benzylidene para toluidine described in German patent 99542.

Fifty grams of selenium were added to this oil and the mixture slowly heated in a nitrate bath to 350°. Some hydrogen selenide evolved with much decomposition. Nothing could be extracted from the melt by hot concentrated hydrochloric acid.

Preparation of Seleno Benzanide—With a view to making this substance the starting point for some work, it was thought advisable to prepare a small amount of seleno benzanide. It has been prepared by several workers, notably Becker and Meyer (10), whose method was followed by the writer.

Phosphorous penta selenide was prepared by fusing molecular quantities of red phosphorus and selenium. Hydrogen selenide was generated by dropping water upon the powdered selenide.

Five grams of benzo nitrile were dissolved in 30 c.c. of absolute alcohol into which dry ammonia gas had been led for a half hour. The hydrogen selenide was bubbled through this solution for an hour, at the end of which time, the alcohol was removed by evaporation in vacuo. The residue was taken up with ether, filtered, and allowed to crystallize. Shining golden needles of the seleno benzanide were obtained which melted at 120° corr. Yield, one gram. Becker and Meyer give a melting point of 115° while G. Hofmann (5) gives a melting point of 126°. Von Dechend (1), who first prepared it, does not give a melting point. The seleno benzanide decomposes gradually on standing.

6-Furfurylidene-amino 2-phenyl benzo selenazole—Commercial furfural was distilled at 69° to 70° and 21.5 mm. and the distillate collected in three portions of 15, 65 and 20 per cent. Only the 65 per cent portion was used in the experimental work. Fourteen grams of 6-amino 2-phenyl benzo selenazole were dissolved in an excess of furfural, 50 grams, and heated on the steam bath for an hour. Upon cooling, the mixture solidified to a mass of yellow needles which were filtered free from most of the furfural and washed with ethyl alcohol. By crystallization from ethyl alcohol gleaming yellow needles melting at 147.5° corr. were

obtained. Yield 13 grams or 75 per cent. The product is soluble in hot carbon tetrachloride, benzene, acetone, and ethyl acetate.

Analysis: Subs. 0.1853; CO_2 , 0.4196; H_2O , 0.0584
Calc. $\text{C}_{18}\text{H}_{12}\text{N}_2\text{OSe}$: C, 61.50; H, 3.42
Found C, 61.76; H, 3.53

Attempted fusion of the fural Schiff base with selenium—Three grams of the Schiff base were fused with 3 grams of metallic selenium in a nitrate bath whose temperature was raised slowly to 330° . Charring and decomposition occurred with no evolution of hydrogen selenide. The Schiff base decomposed at a temperature below the melting point of selenium, 217° . No reaction took place.

Fusion of the fural Schiff base with sulphur—Five grams of sulphur were heated with 5 grams of the Schiff base in an oil bath. Hydrogen sulphide evolved copiously and the melt gradually darkened. The fusion was finished after sixteen hours heating with the bath kept at a temperature under 150° . The melt was pulverized and extracted with hot concentrated hydrochloric acid. A yellow precipitate appeared when these extracts were diluted. This was filtered, washed, and dried. Yield 0.8 gram. The product could not be purified by crystallization from acetic acid, butyl alcohol, benzene, carbon tetrachloride, acetone or ligroin. It is decomposed very easily by heat even when suspended in boiling butyl alcohol.

2, 2'-Diphenyl benzo bis selenazole—6-Benzalamino 2-phenyl benzo selenazole was prepared by condensing benzaldehyde with the amine in alcohol solution. The product after one crystallization from alcohol melted at 157.0° corr. which agrees with the figure given by Bogert and Chen for this Schiff base.

Twenty-five grams of this benzal derivative were fused with 15 grams of selenium on a sand bath for twenty-three hours. By extraction of the melt with concentrated hydrochloric acid, dilution, and filtration, 13 grams of a yellow powder were obtained. By recrystallization from acetic acid and normal butyl alcohol, lemon yellow needles were obtained with a melting point of 217.0° corr. Yield 17 per cent. The selenazole was soluble in hot butyl alcohol and glacial acetic acid, slightly soluble in hot benzene and ethyl alcohol, and insoluble in ether, ethyl acetate and carbon tetrachloride.

Analysis: Subs. 0.1992; CO_2 , 0.4029; H_2O , 0.0482
Calc. $\text{C}_{20}\text{H}_{12}\text{N}_2\text{Se}_2$: C, 54.80; H, 2.74
Found: C, 55.16; H, 2.71

A further proof of the position of the amino group in 6-amino benzo selenazole, is the synthesis of the benzo bis selenazole by

the fusion of 30 grams of dibenzylidene para phenylene diamine with 30 grams of selenium. After twenty-four hours fusion, the melt yielded 7 grams of a crude yellow product on extraction with concentrated hydrochloric acid. By repeated crystallization from glacial acetic acid and butyl alcohol, yellow needles with a melting point of 217.2° to 217.7° corr. were obtained. A mixture of this sample with the benzo bis selenazole prepared from the 6-benzal-amino selenazole melted at 217.2° to 217.7° corr. Yield 1.5 grams or 3 per cent.

Dinitro 2, 2'-diphenyl benzo bis selenazole—One and a half grams of the benzo bis selenazole were dissolved in seven c.c. of conc. sulphuric acid. To this solution, immersed in an ice salt bath, 0.8 c.c. of conc. nitric acid dissolved in 3 c.c. of conc. sulphuric acid was slowly added. After three hours stirring, the mixture was heated on the water bath at 80° for a half hour and then poured into ice water. The precipitate was dried and washed with boiling glacial acetic acid. Yield 1.3 grams or 72 per cent. This was then repeatedly crystallized from nitrobenzene and gave yellow needles darkening around 320° corr. and melting at 332.4° to 333.4° corr.

Analysis: Subs. 0.2014; CO₂, 0.3375; H₂O, 0.0387
Calc. C₂₀H₁₀N₄O₄Se₂: C, 45.45; H, 1.89
Found: C, 45.70; H, 2.13

Mono nitro 2, 2'-diphenyl benzo bis selenazole—Five grams of benzo bis selenazole were dissolved in 17 c.c. of conc. sulphuric acid in an ice salt bath. A mixture of 0.8 c.c. of conc. nitric acid in 7 c.c. of conc. sulphuric acid was slowly added with stirring. After three hours stirring, the mixture was poured into ice water, filtered, washed and dried. After washing with hot acetic acid, four and a half grams of crude nitro derivative remained. One gram of this was crystallized repeatedly from a mixture of two parts of acetic acid and three parts of nitro benzene to form reddish yellow needles melting at 296.1° to 297.1° corr. The nitro derivative is insoluble in ether, ethyl alcohol, butyl alcohol, acetone, and benzene and slightly soluble in acetic acid. It could not be separated from the dinitro derivative.

Mono amino 2, 2'-diphenyl benzo bis selenazole—Three grams of the acetic acid washed mono nitro derivative were boiled with four grams of twenty mesh tin and thirty c.c. of conc. hydrochloric acid until the tin was completely dissolved. The solution was then made strongly alkaline with caustic soda. The precipitate was washed, dried, and extracted with hot aniline. Yield 1 gram or 30 per cent. By repeated crystallizations from aniline and treatment with norite, orange needles were obtained which sintered

around 260° and melted at 279.4° to 281° corr. The amine is insoluble in ether, carbon tetrachloride, ethyl alcohol and butyl alcohol.

Analysis: Subs. 0.2035; CO_2 , 0.3995; H_2O , 0.0570

Calc. $\text{C}_{20}\text{H}_{13}\text{N}_3\text{Se}_2$: C, 52.92; H, 2.87

Found: C, 53.54; H, 3.13

Benzalamino 2, 2'-diphenyl benzo bis selenazole—Five tenths of a gram of the amine were dissolved in 0.8 c.c. of benzaldehyde and 8 c.c. of normal butyl alcohol. After refluxing one hour and allowing the solution to cool, 0.51 grams of gleaming yellow plates were obtained—85 per cent of theory. After recrystallization from toluene the product melted from 233.5° to 235.5° corr.

Analysis: Subs. 0.2126; CO_2 , 0.4732; H_2O , 0.0638

Calc. $\text{C}_{27}\text{H}_{17}\text{N}_3\text{Se}_2$: C, 59.84; H, 3.14

Found: C, 60.70; H, 3.36

Mono acetyl chloride addition product of 2, 2'-diphenyl benzo bis selenazole—Five tenths of a gram of the selenazole were dissolved in 50 c.c. of toluene and 4 c.c. of acetyl chloride added to the hot solution. After standing over night .6 grams of yellow needles were obtained. These were recrystallized from toluene to a melting point of 215.6° to 216.6° corr. or the melting point of the selenazole itself. Acetyl chloride evolved on heating. Yield 0.27 grams or 45 per cent.

Analysis: Subs. 0.1753; CO_2 , 0.3315; H_2O , 0.0470

Calc. $\text{C}_{22}\text{H}_{15}\text{N}_2\text{OClSe}_2$: C, 51.12; H, 2.93

Found: C, 51.57; H, 3.06

Attempted synthesis of tetramethyl di-p-amino seleno benzo-phenone—Twenty-five and a half grams of tetramethyl di-p-amino diphenyl methane—Michler's methane—were fused with 32 grams of selenium in a nitrate bath at a temperature of 325° for 7 hours. Hydrogen selenide evolved copiously. The red tar remaining was soluble in ethyl alcohol, butyl alcohol, and carbon tetrachloride but none of these solvents gave a crystalline product. A vacuum distillation under 21 mm. pressure resulted in distillation of the tar between 150° and 250° with further decomposition. No crystalline compound could be obtained from the tar.

2, 2'-Diphenyl thiazolyl benzo selenazole—Twelve and a half grams of 6-benzalamino 2-phenyl benzo selenazole were fused for 8 hours with 5.2 grams of sulphur flowers in a nitrate bath at 250° – 260° . The melt was pulverized and extracted with hot concentrated HCl. After dilution to precipitate the selenazole, the crude product was crystallized from normal butyl alcohol to give straw colored needles melting at 220.4° to 221.4° corr. Yield 6 grams or 47 per cent. The product was soluble in hot acetic

acid, toluene and aniline, and slightly soluble in hot ethyl alcohol, carbon tetrachloride, and acetone. It could be distilled in vacuo at 345°-350° under 11 mm. pressure.

Analysis: Subs. 0.2029; 0.1186; 0.2148; CO₂, 0.4588;
H₂O, 0.0585; N₂, 8.0 c.c. at 26° and
745.4 mm.; BaSO₄, 0.1340

Calc. C₂₀H₁₂N₂SSe; C, 61.35; H, 3.09;
N, 7.16; S, 8.19

Found: C, 61.67; H, 3.23;
N, 7.30; S, 8.57

Dinitro 2, 2'-diphenyl thiazolyl benzo selenazole—One gram of the selenazole was dissolved in 15 c.c. of concentrated sulphuric acid with cooling. A mixture of 5 c.c. of concentrated sulphuric acid with 0.5 c.c. of concentrated nitric acid was slowly added to the solution in an ice water bath. After standing 2 hours, the mixture was poured into 50 c.c. of ice water and the resultant yellow precipitate filtered, washed, and dried. After washing with hot acetic acid, the crude nitro derivative was recrystallized from nitro benzene to give fine yellow needles melting at 295°-297° corr. Yield 0.6 gram or 50 per cent.

Analysis: Subs. 0.1634; CO₂, 0.3023; H₂O, 0.0380

Calc. C₂₀H₁₀N₄O₄SSe; C, 49.88; H, 2.08

Found: C, 50.46; H, 2.60

Attempted methylation of the thiazolyl selenazole—One and a half grams of the thiazolyl selenazole and 4.5 c.c. of methyl iodide were placed in a sealed tube and maintained at 100° for eight hours. The tube was opened and the contents rinsed out with ethyl alcohol. The crude solid matter was filtered and washed with alcohol. Weight 1.4 grams. After recrystallization from normal butyl alcohol, the product gave straw colored needles melting at 220°-221° corr.,—identical with the melting point of the thiazolyl selenazole used as starting material. No methylation had occurred.

Mono acetyl chloride addition product of the thiazolyl selenazole—One gram of the thiazolyl selenazole was dissolved in 100 c.c. of hot glacial acetic acid and 3 c.c. of acetyl chloride added. The flask was stoppered immediately and allowed to stand over night. The yellow needles so obtained, were filtered, dried, and recrystallized from dry toluene. Yield 0.7 gram or 59 per cent of fine needles melting at 224°-225° corr. When the product melted, acetyl chloride was evolved.

Analysis: Subs. 0.1579; CO₂, 0.3273; H₂O, 0.0472

Calc. C₂₂H₁₆N₂OCISse; C, 56.25; H, 3.20

Found: C, 56.53; H, 3.37

Tetra brom addition product of the thiazolyl selenazole—One gram of the thiazolyl selenazole was dissolved in 30 c.c. of hot chloroform and 2 c.c. of bromine in 5 c.c. of chloroform added to the warm solution. After standing half an hour, the brown needles, which had separated, were filtered, suspended in warm chloroform and again filtered and washed with chloroform. The product slowly decomposed on standing with evolution of bromine. On heating it decomposed with evolution of a gas from 238°-243° corr. Yield 1.6 grams or 85 per cent. A large excess of bromine was necessary to give a pure tetra brom product.

Analysis: Subs. 0.1120; 0.1602; AgBr, 0.1173, 0.1686
 Calc. $C_{20}H_{12}N_2Br_4S_2Se$; Br 44.95
 Found: Br 44.57; 44.79

Bromine was determined by adding the sample to a one per cent solution of sodium bisulphite, boiling for half an hour, filtering out the liberated thiazolyl selenazole, and precipitating the bromide ion as silver bromide from the acidified solution.

Synthesis of a base $C_{27}H_{18}N_2S_2Se$ —In one case 6-benzalamino 2-phenyl benzo selenazole (43 grams) when fused with 15 grams of sulphur at 250°-260° until hydrogen sulphide ceased to evolve, yielded, instead of the thiazolyl benzo selenazole, 16 grams of a disulphuretted selenium compound of a considerably higher molecular weight. Analytical results indicate that this compound has the empirical formula $C_{27}H_{18}N_2S_2Se$, whereas the true thiazolyl selenazole has the formula $C_{20}H_{12}N_2S_2Se$. This compound closely resembles the thiazolyl selenazole in its solubilities and appearances,—being soluble in hot toluene and normal butyl alcohol from which it crystallizes in long lustrous straw colored needles melting at 226.5° corr. The true thiazolyl selenazole melts at 221.5° corr. Repeated efforts to resynthesise this base yielded only the thiazolyl selenazole.

Analysis: Subs. 0.2134; 0.1833; CO_2 , 0.4979, 0.4266; H_2O , 0.0599, 0.0569
 Subs. 0.1503; N, 7.3 c.c. at 26° and 776 mm.
 Subs. 0.3110; $BaSO_4$, 0.2914
 Calc. $C_{27}H_{18}N_2S_2Se$; C, 63.20; H, 3.51; N, 5.45;
 S, 12.45
 Found: C, 63.63; H, 3.13; N, 5.48;
 S, 12.87
 C, 63.47; H, 3.45

Nine grams of the product nitrated with 1.7 c.c. of concentrated HNO_3 and 30 c.c. of concentrated H_2SO_4 in an ice bath for three hours, yielded only 1.5 grams of fine yellow needles by

recrystallization from nitro benzene. These melted at 283° corr. From analytical data this substance is a dinitro derivative of the above compound and corresponds to the empirical formula $C_{27}H_{16}N_4O_4S_2Se$.

Analysis: Subs. 0.2302, 0.1634, 0.1874; CO_2 , 0.4525; H_2O , 0.0583; N_2 , 14.22 c.c. at 22.5° and 744.1 mm.; 16.83 c.c. at 28.5° and 742.2 mm.

Calc. $C_{27}H_{16}N_4O_4S_2Se$; C, 53.70; H, 2.67; N, 9.28

Found: C, 53.61; H, 2.83; N, 9.60, 9.54

Upon reduction with tin and hydrochloric acid, the dinitro-derivative is converted into a diamine with the loss of one sulphur atom, H_2S being evolved in the course of the reduction. Thus, 2 grams of the nitro derivative yielded 0.32 grams of golden needles melting with decomposition around 305° corr. The crude reduction product was recrystallized from aniline.

Analysis: Subs. 0.2017; CO_2 , 0.4710; H_2O , 0.0708

Calc. $C_{27}H_{20}N_4SSe$; C, 63.30; H, 3.91

Found: C, 63.69; H, 3.93

Carbon, hydrogen and nitrogen were determined in the usual way. Sulphur was determined by the Carius method, using a temperature of 210° for five hours, and 240° for two hours.

VITA

Horace Herbert Hopkins was born in 1897 in De Soto, Missouri, where he completed a grammar school education. He then moved to Grand Junction, Colorado, where he graduated from high school with honors. After three years of attendance at Colorado College, Colorado Springs, Colorado, he left school to attend the first Officers Training Camp at Fort Riley, Kansas. After obtaining a second lieutenant's commission from this camp, he was assigned to serve with the eighty-ninth Division in training at Camp Funston, Kansas.

He served overseas as captain of infantry with this division, being regimental intelligence officer, and later, regimental operations officer of the 355th infantry.

After his discharge from the army, he entered Columbia College and received a B.S. degree in 1920.

During the year 1920-1921 he was employed as plant chemist for the Great Western Electrochemical Company of San Francisco. He later became chemist for the Western Meat Company of South San Francisco.

He entered upon graduate work at Columbia University in 1921. He served as assistant in Chemistry for the years 1922-23 and 1923-24.

He is a member of the America Chemical Society, Phi Lambda Upsilon, and Sigma Xi.

CHRONOLOGICAL BIBLIOGRAPHY

- 1—1874—F. V. Dechend, *Ber.*, 7, 1273.
- 2—1886—V. V. Richter, *Ber.*, 19, 1001.
- 3—1887—A. W. Hofmann, *Ber.*, 20, 2262.
- 4—1888—P. Jacobson, *Ber.*, 21, 2623.
- 5—1889—G. Hofmann, *Ann.*, 250, 314.
- 6—1889—O. Hinsberg, *Ber.*, 22, 862.
- 7—1890—Chabrie and Lapique, *Ann. Phys. Chim.*, 6, 120.
- 8—1891—A. Bruere, *J. Anat. Physiol.*, October.
- 9—1898—Farbwerke v. Meister Lucius und Bruning, *D.R.P.* 90542.
- 10—1904—Becker and Meyer, *Ber.*, 37, 2650.
- 11—1907—Clark and Hurlley, *J. Physiol.*, 36, 62.
- 12—1910—C. O. Jones, *J. Biochem.*, 4, 405.
- 13—1911—Wassermann, Keyser and Wassermann, *Deut. Med. Wochschr.*, 37, 2389, and *Chem. Abs.*, 6, 650 (1912).
- 14—1912—Moles and Gomez, *Zeit. Phys. Chem.*, 80, 513.
- 15—1912—Wassermann and Hausmann, *Berl. klin. Wochschr.*, 49, 4, and *Chem. Abs.*, 8, 890.
- 16—1912—Lesser and Weiss, *Ber.*, 45, 1835.
- 17—1912—C. B. Jones, *J. Biochem.*, 6, 106.
- 18—1913—Duhamel and Robere, *Compte Rendu Soc. Biol.*, 72, 670, and *Chem. Abs.*, 7, 2621.
- 19—1913—Duhamel and Juillard, *Compte Rendu Soc. Biol.*, 72, 714, and *Chem. Abs.*, 7, 2621.
- 20—1913—B. G. Duhamel, *Compte Rendu Soc. Biol.*, 72, 742, and *Chem. Abs.*, 7, 2255.
- 21—1913—B. G. Duhamel, *Compte Rendu Soc. Biol.*, 72, 805, and *Chem. Abs.*, 7, 2071.
- 22—1913—F. V. Oefele, *New York Med.*, 97, 78.
- 23—1913—G. Fasiani, *Arch. Sci. Med.*, 36, 436, and *Chem. Abs.*, 7, 1553.
- 24—1913—C. E. Walker, *Lancet*, 182, 1837, and *Chem. Abs.*, 7, 384.
- 25—1913—Farbwerke v. M. Lucius and Bruning, *D.R.P.*, 255, 982.
- 26—1913—F. Heineman, *D.R.P.*, 261, 412.
- 27—1913—A. and E. Wasserman, *D.R.P.*, 261, 556.
- 28—1913—A. and E. Wasserman, *D.R.P.*, 261, 793.
- 29—1913—Farbwerke v. M. Lucius and Bruning, *D.R.P.*, 261, 909.
- 30—1913—Farbenfabriken v. Bayer, *D.R.P.*, 264, 130.
- 31—1913—Farbenfabriken v. Bayer, *D.R.P.*, 264, 941.
- 32—1913—Luzzato and Cissa, *Chem. Zentr.*, 11, 1318.
- 33—1914—H. Bauer, *Ber.*, 47, 1873.
- 34—1914—F. Keyser, *Z. Chemotherapie*, 2188 and *Chem. Abs.*, 8, 2766.
- 35—1914—A. Albert, *D.R.P.*, 273, 073.
- 36—1915—Gerner and Schaleman, *Deut. Med. Wochschr.*, 41, 1213, and *Chem. Abs.*, 10, 72 (1916).
- 37—1915—Ehrlich and Bauer, *Ber.*, 48, 502.
- 38—1915—A. and E. Wasserman, *D.R.P.*, 287, 020.
- 39—1916—P. Karrer, *Ber.*, 49, 579.
- 40—1917—Wrede and Schneider, *Ber.*, 50, 793.
- 41—1918—P. Karrer, *Ber.*, 51, 190.
- 42—1918—Konek and Schleifer, *Ber.*, 51, 842.
- 43—1918—Chem. Fabrik von Heyden, *D.R.P.*, 305, 262.
- 44—1918—Chem. Fabrik von Heyden, *D.R.P.*, 305, 263.
- 45—1919—Hantzlik and Tarr, *J. Pharmacology*, 14, 221.
- 46—1919—B. G. Duhamel, *Compte Rendu Soc. Biol.*, 82, 724, and *Chem. Abs.*, 14, 2883 (1920).
- 47—1919—F. Wrede, *Ber.*, 52, 1756.
- 48—1919—Adams, Kamm, and Marvel, *U. of Ill. Bull.*, 18, No. 6.
- 49—1919—S. Fraerckel, *Die Aromamittel Synthese*, pages 790-797.
- 50—1920—G. Jachrmich, *Phys. Chem. Zeit.*, 107, 300 and *Chem. Abs.*, 15, 104 (1921).
- 51—1920—F. Wrede, *J. Physiol. Chem.*, 112, 1, and *Chem. Abs.*, 15, 2837 (1921).
- 52—1921—Nemec and Kas, *Biochem. Z.*, 114, 12, and *Chem. Abs.*, 16, 1915.
- 53—1921—L. Lilienfeld, *Brit. Patent*, 173, 507.
- 54—1922—Bogert and Abrahamson, *J. Am. Chem. Soc.*, 44, 826.
- 55—1922—Bogert and Chen, *J. Am. Chem. Soc.*, 44, 2352.



RIVERVIEW PRESS, *Inc.*
404 East 36th Street

